NATIONAL GUIDELINE CLEARINGHOUSE™ (NGC™) GUIDELINE SYNTHESIS

SCREENING FOR BREAST CANCER

Guidelines

1. American College of Radiology (ACR). American College of Radiology guidelines for breast cancer screening. AJR Am J Roentgenol 1998 Jul;171(1):29-33. [61 references]
2. Scottish Intercollegiate Guidelines Network (SIGN). Breast cancer in women. A national clinical guideline. Edinburgh (Scotland): Scottish Intercollegiate Guidelines Network (SIGN), Scottish Cancer Therapy Network; 1998 Oct. 64 p. (SIGN publication; no. 29). [216 references]
3. Royal New Zealand College of General Practitioners (RNZCGP). Early detection of breast cancer. Wellington (New Zealand): Royal New Zealand College of General Practitioners; 1999. 61 p. [176 references]
4. Canadian Task Force on Preventive Health Care (CTFPHC).
    - Preventive health care, 2001 update: screening mammography among women aged 40-49 years at average risk of breast cancer. CMAJ 2001 Feb 20;164(4):469-76. [76 references]
    - Preventive health care, 2001 update: should women be routinely taught breast self-examination to screen for breast cancer? CMAJ 2001 Jun 26;164(13):1837-46. [78 references]
5. Kaiser Permanente-Southern California (KPSC). Breast cancer screening. Pasadena (CA): Kaiser Permanente Southern California; 2001 Apr. 4 p. [84 references]
6. U.S. Preventive Services Task Force (USPSTF). Screening for breast cancer: recommendations and rationale Ann Intern Med 2002 Sep 3;137(5 Part 1):344-6. [10 references]

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GUIDELINE CONTENT COMPARISON

INTRODUCTION:

A direct comparison of, ACR, SIGN, RNZCGP, CTFPHC, KPSC, and USPSTF recommendations for screening asymptomatic women for breast cancer is provided in the tables below. Table 1 gives a broad overview of the six guidelines; Table 2 details the recommendations for mammographic screening as well as for other screening strategies; Table 3 specifies the potential benefits and harms associated with breast cancer screening. SIGN's guideline includes recommendations for diagnosis and clinical management of women with breast cancer; these recommendations will be covered in a separate NGC Guideline Synthesis. RNZCGP's guideline also includes recommendations for risk assessment, diagnostic recommendations for women with symptoms suggestive of breast cancer, and information for cultural considerations for Maori women.

The evidence supporting the major recommendations is also identified, with the definitions of the rating schemes used by SIGN, RNZCGP, CTFPHC, and USPSTF included in the last row of Table 2.

Listed below are common abbreviations used within the tables and discussions:

- ACR, American College of Radiology
- BSE, breast self-examination
- CBE, clinical breast examination
- CTFPHC, Canadian Task Force on Preventive Health Care
- DCIS, Ductal carcinoma in situ
- KPSC, Kaiser Permanente-Southern California
- RNZCGP, Royal New Zealand College of General Practitioners
- SIGN, Scottish Intercollegiate Guidelines Network
- USPSTF, United States Preventive Services Task Force

TABLE 1: COMPARISON OF SCOPE AND CONTENT	
ACR (1998)	Objective: To revise ACR screening guidelines for breast cancer, in light of mounting evidence that women younger than 50 years old have a shorter lead time for mammographic detection of breast cancer Target Population: • United States • Women who are 40 years old or older without signs or symptoms of breast cancer • Women of any age at high risk of breast cancer, but

	without signs or symptoms of breast cancer Intended Users: Physicians Interventions and Practices Considered: • Annual mammography • Clinical breast examination • Breast self-examination Excluded Topics: None
SIGN (1998)	Objectives: To provide evidence-based recommendations about best clinical practice to assist cancer centers, cancer units and primary care to produce their own local guidelines for the management of patients with breast cancer Target Population: • Scotland • Women of all ages Intended Users: Physicians; Nurses; Nurse Practitioners; Physician Assistants; Allied Health Care Practitioners; Clinical Laboratory Personnel Interventions and Practices Considered: • Mammography • Clinical breast examination • Breast self-examination • Referral to a breast specialist • Treatment (surgical, pharmacological, psychosocial) • Follow up strategies for patient and local general practitioners • Nursing care Excluded Topics: None
RNZCGP (1999)	Objectives: • To help primary care providers provide consistent advice to women about the risk factors for and the early detection and diagnosis of breast cancer • To provide information about cultural considerations for Maori, which may be useful for improving the service effectiveness that primary care providers can offer

	Target Population:
	
	• New Zealand
	• Asymptomatic and symptomatic women
	  • Women aged 50-74 years without symptoms suggestive of breast cancer
	  • High-risk asymptomatic women aged 40 and over
	  • Women with symptoms suggestive of breast cancer
	  • Maori women
	
	Intended Users: Nurse Practitioners; Nurses; Physicians
	
	Interventions and Practices Considered:
	
	• Risk assessment (identify risk factors for developing breast cancer, such as gender, age, family history, medical history, radiation exposure; genetic testing for BRCA 1 and 2 genes)
	• Screening
	  • Mammography alone or with clinical breast examination (CBE)
	  • Breast self-examination (BSE)
	• Diagnostic procedures (the triple test: CBE, diagnostic mammography, fine needle aspiration biopsy; diagnostic ultrasound; core biopsy; other diagnostic modalities)

CTFPHC (2001 Updates)	Objective: To make recommendations on (1) screening mammography in asymptomatic Canadian women aged 40 to 49 years at average risk of breast cancer and (2) teaching of breast self-examination in asymptomatic women of all ages in the general population Target Population: • Canada • Asymptomatic women aged 40 to 49 at average risk of breast cancer (mammography screening) • Asymptomatic women of all ages in the general population (routine teaching of breast self-examination) Intended Users: Physicians; Nurse Practitioners; Physician Assistants; Allied Health Care Practitioners Interventions and Practices Considered: • Mammographic breast cancer screening • Routine teaching of breast self-examination as part of the periodic health examination

	Excluded Topics: Clinical breast examination, mammographic screening in populations other than asymptomatic women aged 40-49 years

KPSC (2001)	Objective: To assist physicians and other health care professionals in counseling women of all ages on the benefits and harms of breast cancer screening exams
	
	Target Population:
	
	• United States
	• Asymptomatic women in the following age ranges: under 40 years, 40 to 49 years, 50 to 69 years, 70 to 74 years, or 75 years and older
	• Asymptomatic women of any age with any of the following selected risk factors:
	  • Personal history of breast cancer
	  • Breast biopsy showing atypical hyperplasia, lobular neoplasia (lobular carcinoma in situ) or histology unknown
	  • First-degree relative (mother or sister) diagnosed with breast cancer at age 50 or older
	  • First-degree relative (mother, sister, or daughter) diagnosed with breast cancer before age 50
	
	Intended Users: Allied Health Care Practitioners; Physicians
	
	Interventions and Practices Considered:
	
	• Mammography
	• Clinical breast examination
	• Breast self-examination

USPSTF (1996, revised 2002)	Objective: To update the 1996 recommendations on screening for breast cancer in women at average or high risk Target Population: • United States • Women 40 years and older Intended Users: Physicians; Nurses; Nurse Practitioners; Physician Assistants; Allied Health Care Practitioners; Students Interventions and Practices Considered: • Routine screening with mammography alone or mammography and annual clinical breast examination

	• Clinical breast examination alone • Breast self-examination Excluded Topics: None

TABLE 2: COMPARISON OF RECOMMENDATIONS FOR BREAST CANCER SCREENING	
COMPARISON OF RECOMMENDATIONS FOR MAMMOGRAPHIC SCREENING	
ACR (1998)	Women 40 to 49 years old: Annual mammographic screening is recommended. Women 50 to 69 years old: Annual mammographic screening is recommended. Women ≥70 years old: It is unclear at what age, if any, women cease to benefit from screening mammography. Because this age is likely to vary with the individual depending on her overall health, the decision as to when to stop routine mammography screening should be made on an individual basis by each woman and her physician. Women at increased risk for breast cancer: Mammographic screening before the age of 40 years may benefit women who are at high risk for breast cancer, although no available outcome data have assessed this practice.
SIGN (1998)	Women <40 years old at high risk for breast cancer[1]: Biennial mammography (and annual clinical examination) is recommended (grade C recommendation). Women 40 to 50 years old at high risk for breast cancer[1]: Annual mammography (and clinical examination) is recommended (grade C recommendation). Women 50 to 64 years old: Women in this age group are invited every three years for screening through the National Health Service Breast Screening Programme. All members of the primary care team should be aware of the concerns women have about breast screening, and should encourage attendance (grade C recommendation). Women >64 years old: Women over the age of 64 are encouraged to continue to attend the National Health Service

	Breast Screening Programme every three years although they are not routinely invited. All members of the primary care team should be aware of the concerns women have about breast screening, and should encourage attendance (grade C recommendation). Women 50+ years old at high risk for breast cancer[1]: Depending on the risk, recommendations include either discharge to the National Health Service Breast Screening Programme or continuance of more frequent screening (grade C recommendation). Note: Women with lobular carcinoma in situ (LCIS) or severe atypical hyperplasia are at higher relative risk (of about 4) of breast cancer and should have annual or biennial mammography. [1]High risk for breast cancer due to familial breast cancer including: (1) One first degree relative[2] with bilateral breast cancer or breast and ovarian cancer; or (2) One first degree relative with breast cancer diagnosed under the age of 40 years or one first degree male relative with breast cancer diagnosed at any age; or (3) Two first or second degree relatives[2] with breast cancer diagnosed under the age of 60 years or ovarian cancer at any age on the same side of the family; or (4) Three first or second degree relatives with breast or ovarian cancer on the same side of the family. [2]In this context, a first degree female relative is mother, sister, or daughter. A second degree female relative is grandmother, granddaughter, aunt, or niece.
RNZCGP (1999)	Mammography is the principle screening procedure for breast cancer (in women with no symptoms). • For women under age 40, screening mammography is not recommended • For women aged 40-49, annual routine mammography is not advised unless they are higher risk (as defined in the guideline). [Level I] • For higher risk women (as defined in the guideline) over the age of 40, annual mammography is recommended. [Level III-2] • For women aged 50-74 two-yearly mammography is recommended. [Level I]
CTFPHC (2001 Updates)	Women 40 to 49 years old: Current evidence regarding the effectiveness of screening mammography does not suggest the inclusion of the maneuver in, or its exclusion from, the periodic

	health examination of women aged 40 to 49 at average risk of breast cancer (grade C recommendation). Upon reaching the age of 40, Canadian women should be informed of the potential benefits and risks of screening mammography and assisted in deciding at what age they wish to initiate the maneuver. Women 50 to 69 years old: The guideline update on mammography screening does not address this population group. Women ≥ 70 years old: The guideline update on mammography screening does not address this population group. Women at increased risk for breast cancer: The guideline update on mammography screening does not address this population group.
KPSC (2001)	Asymptomatic women ages 40 to 49: Should be offered screening with mammography every one to two years. These women should be: 1) informed of the benefits and harms of mammography; and 2) encouraged to make a personal decision, in collaboration with their physician, about whether to be screened and how frequently. (Evidence based) Note: Any woman between age 40 and 49 who requests screening should be given a mammogram. Asymptomatic women ages 50 to 69: Should be screened with mammography at least every two years beginning at age 50. (Evidence based) Asymptomatic women ages 70 to 74: Should be 1) informed of the potential benefits and harms of mammography; and 2) encouraged to make a personal decision in collaboration with their physician about whether to be screened and how frequently. (Evidence based) Asymptomatic women ages 75 and older: Should be 1) informed of the lack of evidence for benefits and harms of mammography; and 2) encouraged to make a personal decision in collaboration with their physician about whether to be screened and how frequently. (Consensus based) Note: Any woman age 70 or older who requests screening should be given a mammogram. Routine mammography screening is not recommended for asymptomatic women under age 40. (Consensus based)

	Women with selected risk factors: Annual mammography screening is recommended for women with the selected risk factors. (Consensus based). Risk factors and screening recommendations are as follows: • Personal history of breast cancer (including ductal carcinoma in situ) - begin screening after diagnosis. • Breast biopsy showing atypical hyperplasia, lobular neoplasia (lobular carcinoma in situ), or histology unknown - begin screening after diagnosis. • Mother or sister diagnosed with breast cancer at age 50 or older - begin screening at age 40. • Mother, sister, or daughter diagnosed with breast cancer before age 50 - begin screening at age 35. • Blood relative with a confirmed, clinically significant alteration in a BRCA gene (associated with increased risk for the development of breast cancer) - begin screening after documentation of genetic alteration in the patient.
USPSTF (1996, revised 2002)	• For women aged 40 and over, the U.S. Preventive Services Task Force recommends screening mammography, with or without clinical breast examination, every 1-2 years. (B recommendation). Clinical Considerations • The precise age at which the benefits from screening mammography justify the potential harms is a subjective judgment and should take into account patient preferences. Clinicians should inform women about the potential benefits (reduced chance of dying from breast cancer), potential harms (e.g., false-positive results, unnecessary biopsies), and limitations of the test that apply to women their age. Clinicians should tell women that the balance of benefits and potential harms of mammography improves with increasing age for women between the ages of 40 and 70. • Women who are at increased risk for breast cancer (e.g., those with a family history of breast cancer in a mother or sister, a previous breast biopsy revealing atypical hyperplasia, or first childbirth after age 30) are more likely to benefit from regular mammography than women at lower risk. The recommendation for women to begin routine screening in their 40s is strengthened by a family history of breast cancer having been diagnosed before menopause. • For women aged 50 and older, there is little evidence to suggest that annual mammography is more effective than mammography done every other year. • For women aged 40-49, available trials also have not

	reported a clear advantage of annual mammography over biennial mammography. Nevertheless, some experts recommend annual mammography based on the lower sensitivity of the test and on evidence that tumors grow more rapidly in this age group. • The precise age at which to discontinue screening mammography is uncertain. Only two randomized controlled trials enrolled women older than 69, and no trials enrolled women older than 74. Older women face a higher probability of developing and dying from breast cancer but also have a greater chance of dying from other causes. Women with comorbid conditions that limit their life expectancy are unlikely to benefit from screening.
COMPARISON OF RECOMMENDATIONS REGARDING CLINICAL BREAST EXAMINATION AND BREAST SELF-EXAMINATION	
ACR (1998)	• Monthly breast self-examination and annual clinical breast examination should be performed, although their benefit is scientifically unproven.
SIGN (1998)	• Women should be encouraged to become aware of the feel and shape of their breasts through breast self-examination (BSE), so that they are familiar with what is normal for them and to report any change from normal to their general practitioner (grade C recommendation). • Clinical examinations are recommended annually in women younger than 40 years of age and between the ages of 40 to 50 who are at high risk of breast cancer[1] (grade C recommendation). Women ages 50+ years, depending on the degree of risk [1], should either be discharged to National Health Service Breast Screening Programme or continue more frequent screening. All screening of individuals at high risk[1] should be part of a clinically audited program (grade C recommendation). [1] High risk for breast cancer due to familial breast cancer including: (1) One first degree relative[2] with bilateral breast cancer or breast and ovarian cancer; or (2) One first degree relative with breast cancer diagnosed under the age of 40 years or one first degree male relative with breast cancer diagnosed at any age; or (3) Two first or second degree relatives[2] with breast cancer diagnosed under the age of 60 years or ovarian cancer at any age on the same side of the family; or (4) Three first or second degree relatives with breast or ovarian cancer on the same side of the family. [2] In this context, a first degree female relative is mother, sister,

	or daughter. A second degree female relative is grandmother, granddaughter, aunt, or niece.
RNZCGP (1999)	• Clinical breast examination may be used in conjunction with mammography screening. [Level I] Mammography is more sensitive than CBE in screening asymptomatic women, but the sensitivity of both CBE and mammography combined is greater than either alone. • While there have been many studies to date, methodological problems in many and the variable findings make it unclear as to any benefit that might accrue from BSE in asymptomatic women. As a result, it is suggested that (1) women, especially those over 40, should be advised to regularly look and feel for breast changes, rather than follow a systematic method of examination; (2) primary care providers should advise women that changes could indicate cancer is present and to report any changes promptly to their doctor; (3) all women who have symptoms suggestive of breast cancer should be encouraged to consult their doctor regardless of the results of recent mammograms.
CTFPHC (2001 Updates)	• Women aged 50 to 69: Because there is fair evidence of no benefit, and good evidence of harm, there is fair evidence to support the recommendation that routine teaching of breast self-examination (BSE) be excluded from the periodic health examination [grade D recommendation, Level I, II-1, II-3 evidence]. • Women aged 40 to 49: Because there is fair evidence of no benefit, and good evidence of harm, there is fair evidence to support the recommendation that routine teaching of BSE be excluded from the periodic health examination [grade D recommendation, level I, II-1, II-3 evidence]. While the evidence indicates no benefit from routine instruction, some women will request teaching in BSE. The pros and cons should be discussed with the woman, and if breast self-examination is taught, care must be taken to ensure that breast self-examination is conducted in a proficient manner. Note: There is insufficient evidence for effectiveness of routine teaching of BSE in women younger than 40 or older than 70 years, thus precluding making recommendations for teaching breast self-examination to women in these age groups.
KPSC (2001)	• Women should be 1) informed of the lack of evidence of benefit from breast self-examination; and 2) encouraged to make a personal decision, in collaboration with their physician, about whether to perform breast self-

	examination and how frequently. (Evidence based) • All women should be counseled to seek immediate medical attention upon detection of a breast lump. (Consensus based) • Clinical breast examination by a health care provider is recommended at least every 2 years for women age 50 to 69, and at least every 3 years for women age 20 to 49 and 70 and older. (Consensus based)
USPSTF (1996, revised 2002)	• The evidence is insufficient to recommend for or against routine clinical breast examination (CBE) alone to screen for breast cancer. (I recommendation) • The evidence is insufficient to recommend for or against teaching or performing routine breast self-examination (BSE). (I recommendation.) • Clinicians who advise women to perform BSE or who perform routine CBE to screen for breast cancer should understand that there is currently insufficient evidence to determine whether these practices affect breast cancer mortality, and that they are likely to increase the incidence of clinical assessments and biopsies.
EVIDENCE RATING SCHEMES	
ACR (1998)	Not applicable
SIGN (1998)	Grades of Recommendations: A - Requires at least one randomised controlled trial as part of a body of literature of overall good quality and consistency addressing the specific recommendation. (Evidence levels Ia, Ib) B - Requires the availability of well conducted clinical studies but no randomised clinical trials on the topic of recommendation. (Evidence levels IIa, IIb, III) C - Requires evidence obtained from expert committee reports or opinions and/or clinical experiences of respected authorities. Indicates an absence of directly applicable clinical studies of good quality. (Evidence level IV) Levels of Evidence: Ia - Evidence obtained from meta-analysis of randomized controlled trials.

	Ib - Evidence obtained from at least one randomized controlled trial. IIa - Evidence obtained from at least one well-designed controlled study without randomization. IIb - Evidence obtained from at least one other type of well-designed quasi-experimental study. III - Evidence obtained from well-designed non-experimental descriptive studies, such as comparative studies, correlation studies and case studies. IV - Evidence obtained from expert committee reports or opinions and/or clinical experiences of respected authorities.
RNZCGP (1999)	Levels of Evidence: I Evidence obtained from systematic review of all relevant randomised controlled trials (RCTs). II Evidence obtained from at least one properly designed RCT. III-1 Evidence obtained from well designed controlled trials without randomisation. III-2 Evidence obtained from well designed cohort or case controlled analytic studies, preferably from more than one centre or research group. III-3 Evidence obtained from multiple time-series with or without the intervention. Dramatic results in uncontrolled experiments such as the introduction of penicillin treatment in the 1940s could be regarded as this type of evidence. IV-1 Evidence from descriptive studies including case series, case reports and cross-sectional studies. IV-2 Published policies, recommendations or opinions of recognised experts, organisations, or learned colleagues. Including endorsement of Level IV-3 evidence by recognised bodies. IV-3 Consensus opinion of the working party not endorsed formally by recognised bodies. N/A Not applicable - not possible to apply a level of evidence.

CTFPHC (2001 Updates)	Levels of evidence: I - Evidence from at least one properly randomized controlled trial. II-1 - Evidence from well-designed controlled trials without randomization. II-2 - Evidence from well-designed cohort or case-control analytic studies, preferably from more than one centre or research group. II-3 - Evidence from comparisons between times or places with or without the intervention. Dramatic results from uncontrolled experiments could also be included here. III - Opinions of respected authorities, based on clinical experience, descriptive studies or reports of expert committees. Grades of recommendations: A - Good evidence to support the recommendation that the condition or maneuver be specifically considered in a periodic health examination B - Fair evidence to support the recommendation that the condition or maneuver be specifically considered in a periodic health examination C - Insufficient evidence regarding inclusion of the condition or maneuver in, or its exclusion from, a periodic health examination, but recommendations may be made on other grounds D - Fair evidence to support the recommendation that the condition or maneuver be specifically excluded from a periodic health examination E - Good evidence to support the recommendation that the condition or maneuver be specifically excluded from a periodic health examination
KPSC (2001)	Not applicable
USPSTF (1996, revised 2002)	USPSTF grades the quality of the overall evidence on a 3-point scale (good, fair, or poor). Good

	Evidence includes consistent results from well-designed, well-conducted studies in representative populations that directly assess effects on health outcomes. Fair Evidence is sufficient to determine effects on health outcomes, but the strength of the evidence is limited by the number, quality, or consistency of the individual studies; generalizability to routine practice; or indirect nature of evidence on health outcomes. Poor Evidence is insufficient to assess the effects on health outcomes because of limited number of power of studies, important flaws in their design or conduct, gaps in the chain of evidence, or lack of information on important health outcomes. The USPSTF grades its recommendations according to one of five classifications (A, B, C, D, or I), reflecting the strength of evidence and magnitude of net benefit (benefits minus harms). A The USPSTF strongly recommends that clinicians routinely provide [the service] to eligible patients. (The USPSTF found good evidence that [the service] improves important health outcomes and concludes that benefits substantially outweigh harms.) B The USPSTF recommends that clinicians routinely provide [the service] to eligible patients. (The USPSTF found at least fair evidence that [the service] improves health outcomes and concludes that benefits outweigh harms.) C The USPSTF makes no recommendation for or against routine provision of [the service]. (The USPSTF found at least fair evidence that [the service] can improve health outcomes but concludes that the balance of benefits and harms it too close to justify a general recommendation.) D The USPSTF recommends against routinely providing [the service] to asymptomatic patients. (The USPSTF found at least fair evidence that [the service] is ineffective or that harms outweigh benefits.) I The USPSTF concludes that the evidence is insufficient to recommend for or against routinely providing [the service].

	(Evidence that [the service] is effective is lacking, of poor quality, or conflicting and the balance of benefits and harms cannot be determined.)

TABLE 3	
POTENTIAL BENEFITS ASSOCIATED WITH BREAST CANCER SCREENING	
ACR (1998)	Mortality rate reduction of at least 25% for women 50 years old and older, and at least 18% for women 40 to 49 years old have been reported.
SIGN (1998)	Optimal screening for (and management of) breast cancer can increase the overall and disease-free survival rate. Meta-analysis of the international screening mammography trials shows statistically significant mortality reduction of 18-29% in the 40 to 49 year age group.
RNZCGP (1999)	• Breast screening reduces breast cancer mortality by 20% to 38% in women aged between 50 and 64 years. It has been estimated 480 lives could be saved over the first five years if mammography screening is provided to the entire female population aged 50-69. • Screening mammography has a high sensitivity (80-95%) and specificity (93-95%) and both of these measures generally increase with a patient's age. Regular two-yearly screening mammography results in a reduction of breast cancer mortality by approximately 30% for women aged 40-74. Specifically, mortality is reduced 26-34% in women aged over 65 and 20-38% in women aged 50-64 by two-yearly mammography screening.
CTFPHC (2001 Updates)	Potential reduction in mortality rates: Relative risk reduction of 18% to 45% for breast cancer mortality at 10 years was shown in two trials and one meta-analysis; no benefit was shown in six other trials. (The only trial that enrolled Canadian women failed to show an effect of screening mammography, possibly because of low power.) Other positive effects of screening mammography in women ages 40 to 49: • Detection of tumour at earlier stage (possibly predictive of less toxic treatment) • Improved cosmesis • Reassurance (72% of cases)

	• Reduced anxiety about cancer at time of screening
KPSC (2001)	The effectiveness of screening tests in reducing mortality from breast cancer varies by the type of test and a woman's age. <u>Mammography</u> Women Age 40 to 49 - Mammography has a sensitivity of about 75% in this group. While the evidence shows a trend toward a net health benefit of screening, e.g., a meta-analysis of 10 large, controlled trials found a 15% (0.85, 95% C.I. 0.68-1.06) relative reduction in mortality risk in screened vs. unscreened women, the results were not statistically significant. Of the 10 studies in the meta-analysis, only 2 show a statistically significant benefit of mammography screening. Women Age 50 to 69 - Mammography is most sensitive (approximately 90%), and offers the greatest survival benefit among women age 50-69. A meta-analysis of 11 large, controlled trials of mammography screening found a statistically significant 25% (0.75, 95% C.I. 0.67-0.84) relative reduction in mortality risk in screened vs. unscreened women in this age group. Another meta-analysis of 5 controlled trials found that the reduction in mortality remains when analyses are conducted by age-specific subgroups (50-59 and 60-69). Women Age 70 to 74 - The evidence also reveals uncertainty of a net health benefit of mammography screening in this group. While a meta-analysis of 2 large, randomized controlled trials found a 26% (0.74, 95% C.I. 0.47-1.16) relative reduction in mortality in screened vs. unscreened women, the results were not statistically significant. Women 75 and Older - Only one of the large, controlled trials of mammography screening included women older than age 75 at the onset of screening, but the reported data does not allow for age-specific analysis. Thus, the age at which screening is no longer useful remains unknown. However, the incidence of breast cancer in women advances with age and is highest in women age 75 and older. Women Younger Than 40 - The incidence of breast cancer is lowest in women under 40. Of the large, controlled trials, only one included women age 35 or older, but the study did not report age-specific data. Results from the major trials indicate that the benefit of mammography is lower in women age 40-49 when compared to women age 50-69. Consequently, it can be expected that any benefit of screening in women under age 40 would be lower than the 15% benefit found in women age 40-

	49, which was not statistically significant. Breast Self-examination (BSE) A meta-analysis of 6 large controlled trials found no reduction in the relative risk of mortality in women performing BSE vs. those not performing BSE (0.94, 95% C.I. 0.83-1.06). Clinical Breast Examination (CBE) There is no direct, but some indirect, evidence that CBE decreases breast cancer mortality. CBE has an overall sensitivity of 54%, which varies with the patient's age and size of the mass, as well as the provider's skill in clinical examination.
USPSTF (1996, revised 2002)	The USPSTF found fair evidence that mammography screening every 12-33 months significantly reduces mortality from breast cancer. Evidence is strongest for women aged 50-69, the age group generally included in screening trials. For women aged 40-49, the evidence that screening mammography reduces mortality from breast cancer is weaker, and the absolute benefit of mammography is smaller, than it is for older women. Most, but not all, studies indicate a mortality benefit for women undergoing mammography at ages 40-49, but the delay in observed benefit in women younger than 50 makes it difficult to determine the incremental benefit of beginning screening at age 40 rather than at age 50. The absolute benefit is smaller because the incidence of breast cancer is lower among women in their 40s than it is among older women. The USPSTF concluded that the evidence is also generalizable to women aged 70 and older (who face a higher absolute risk of breast cancer) if their life expectancy is not compromised by comorbid disease. The absolute probability of benefits of regular mammography increases along a continuum with age, whereas the likelihood of harms from screening (false-positive results and unnecessary anxiety, biopsies, and cost) diminishes from ages 40-70. The balance of benefits and potential harms, therefore, grows more favorable as women age. The precise age at which the potential benefits of mammography justify the possible harms is a subjective choice.
POTENTIAL HARMS ASSOCIATED WITH BREAST CANCER SCREENING	
ACR (1998)	False positive interpretations: Recalling women for additional examination after screening mammography and ultimately recommending a breast biopsy for some is a source of anxiety, inconvenience, and--in the case of biopsy--

	discomfort and occasional scarring. Radiation-induced breast cancer: Although not zero, women have little risk from annual mammography performed at current low radiation doses. Overtreatment: Some lesions that may never be lethal are detected at screening, undergo biopsy, and are classified by pathologists as cancer. Because as yet no reliable methods exist for distinguishing these lesions from tumors with metastatic potential, some women will be overtreated. Diagnostic delay: False reassurance from a previous mammogram may result in delay in diagnosis of breast cancer if the woman or her physician ignores the development of a palpable mass between screening examinations.
SIGN (1998)	Radiation risk from mammography: It is thought that ionizing radiation increases the risk of breast cancer development after a latent period of 10 years, that the risk is cumulative, and that the risk is greatest for adolescent exposure and decreases with increasing age at exposure. In those aged over 50, the risk of cancer induction is, very approximately, 1:100000 per single view examination. The average dose per examination (single view per breast) is approximately 2mGy, the dose being dependent on breast thickness and exposure factors used.
RNZCGP (1999)	False positives. These can lead to unnecessary investigations ranging from repeat mammography to ultrasound, fine needle aspiration biopsy and/or biopsy. There is a significant false positive rate for mammography screening (0.9-6.5%), which substantially contributes to the costs associated with screening. In New Zealand, the risk of a false positive for a woman at some point during a 20-year screening programme (aged 50-69) has been calculated at 34%. False negatives. As with any investigation a negative result may occur even though cancer is present. The sensitivity of screening mammography is 86-94% depending on age. Thus the false negative rate is 6-14%. Over-treatment: There is a potential for a screening programme to detect a cancer in a woman who might never have presented clinically before dying from another cause. Thus screening may increase morbidity while not reducing mortality.
CTFPHC (2001 Updates)	Negative effects of screening mammography: • Radiation-induced carcinoma

	• Unnecessary biopsies (0.6% to 0.9% of cases in Sweden, 5% to 9% of cases in U.S.) • Psychological stress of call-back (40% of cases) • Additional x-ray films (3% to 13% of cases in Sweden, 56% of cases in U.S.) • Possible false reassurance or false positive results
KPSC (2001)	<u>Mammography</u> Women 40-49: The positive predictive value of an abnormal screening mammogram is only 5% for women age 40 to 49 who have an average risk of breast cancer. It is estimated that approximately 30% of women who begin biennial screening mammography at age 40 will have at least one false-positive mammogram by age 49. The sensitivity of screening mammography in women age 40 to 49 is approximately 75%. With this level of performance, 20-25% of women with breast cancer in their 40s may be falsely reassured by a false-negative mammogram result. Women 50-69: The positive predictive value of an abnormal screening mammogram is 10-15% for women over the age of 50 who have average risk of breast cancer. It is estimated that approximately 24% of women who begin biennial screening mammography at age 50 will have at least one false-positive mammogram within a 10-year screening period. The sensitivity of screening mammography in women over 50 is approximately 90%. With this level of performance, 10% of women with breast cancer may be falsely reassured by a false-negative mammogram result. Radiation: There is no clear evidence that accumulated radiation from mammography increases the risk of breast cancer.
USPSTF (1996, revised 2002)	False positives: Similar to other cancer screening tests, the large majority (80% to 90%) of abnormal screening mammograms or CBEs are false-positives. These may require follow-up testing or invasive procedures such as breast biopsy to resolve the diagnosis, and can result in anxiety, inconvenience, discomfort, and additional medical expenses. The consequences of false-positive mammograms are uncertain. Most, but not all, studies report increased anxiety from an abnormal mammogram. At the same time, some studies report that women in the United States may be willing to accept a relatively high number of false-positive results in the population in return for the benefits of mammography. Studies do not indicate that false-positive results diminish

	adherence to subsequent screening. False negatives: False-negatives also occur with mammograms and CBE. Although false-negative results might provide false reassurance, the USPSTF found no data indicating these led to further delays in diagnosis. Over-diagnosis and treatment: Some experts view the over-diagnosis and treatment of ductal carcinoma in situ (DCIS) as a potential adverse consequence of mammography. Although the natural history of DCIS is variable, many women in the United States are treated aggressively with mastectomy or lumpectomy and radiation. Given the dramatic increase in the incidence of DCIS in the past two decades (750%) and autopsy series suggesting that there is a significant pool of DCIS among women who die of other causes, screening may be increasing the number of women undergoing treatment for lesions that might not pose a threat to their health. Radiation risks. A final potential concern about mammography is radiation-induced breast cancer, but there are few data to directly assess this risk. A 1997 review, using risk estimates provided by the Biological Effects of Ionizing Radiation report of the National Academy of Sciences, estimated that annual mammography of 100,000 women for 10 consecutive years beginning at age 40 would result in up to 8 radiation-induced breast cancer deaths.

GUIDELINE CONTENT COMPARISON

The American College of Radiology (ACR), the Scottish Intercollegiate Guidelines Network (SIGN), the Royal New Zealand College of General Practitioners (RNZCGP), the Canadian Task Force on Preventive Health Care (CTFPHC), Kaiser Permanente-Southern California (KPSC), and the U.S. Preventive Services Task Force (USPSTF) present recommendations for screening mammography for breast cancer based on evidence available at the time of each report and provide explicit reasoning behind their judgments. CTFPHC's guideline update on screening mammography limits its recommendations to women aged 40-49 years at average risk of breast cancer. The KPSC, RNZCGP, USPSTF, SIGN, and CTFPHC guidelines also evaluate other screening interventions for breast cancer, such as teaching breast self-examination in the periodic health examination and clinical breast examination. SIGN’s screening recommendations are less focused on routine screening (no graded recommendations are offered for routine screening) compared to the other guidelines, and more focused on screening women who have been identified as being at high-risk for breast cancer (graded recommendations are offered). SIGN's guideline is broader in scope than any of the other guidelines, and includes recommendations for diagnosis, treatment, and management of breast cancer. The scope of the RNZCGP guideline is also somewhat broader than the others in that it provides recommendations for

assessing risk factors for breast cancer and for diagnostic investigations in symptomatic women. In addition, RNZCGP provides recommendations for clinical considerations for the Maori population of New Zealand.

Areas of Agreement

Mammographic Screening for Women Aged 50-69 Years

ACR, RNZCGP, KPSC, and USPSTF agree that routine screening mammography is inicated in women aged 50 to 69. USPSTF recommends annual or biennial screening, while ACR recommends annual screening, and RNZCGP and KPSC recommend biennial screening. Although SIGN does not make recommendations for routine screening in women aged 50 to 64 years, women in this age group are invited every three years for screening mammography by the National Health Service, and physicians are reminded to encourage attendance. CTFPHC does not offer recommendations for this age group in its 2001 guideline update.

Screening of Women with Selected Risk Factors for Breast Cancer

Although not all of the organizations give specific recommendations for screening of high-risk women, there is general agreement concerning the value of screening among those that do offer recommendations. SIGN, RNZCGP, and KPSC agree that women over age 40 at high risk for breast cancer should receive annual mammographic screening. USPSTF states that the recommendation for women to begin routine screening in their 40s is "strengthened by a family history of breast cancer having been diagnosed before menopause." SIGN and KPSC also give specific recommendations for regular screening of high-risk women under age 40. ACR states that mammographic screening before age 40 may benefit women at high risk for breast cancer.

Mammographic Screening of Older Women ($\geq$70 years)

The organizations that address this older population group generally agree that there is no clear age at which mammographic screening should be terminated. Rather, the decision to screen should be made on an individual basis, taking into account personal preferences and weighing individual risks and benefits.

Areas of Differences

Mammographic Screening of Women Aged 40-49 Years at Average Risk of Breast Cancer

The value of routine screening of women aged 40-49 years at average risk of breast cancer is an area of controversy among the guideline groups. Much of the controversy is due to the quality and interpretation of clinical trial data regarding mortality benefits of screening.

Two groups (ACR and USPSTF) recommend routine screening in this age group. ACR recommends annual screening, and USPSTF recommends either annual or biennial screening. While both guideline groups acknowledge that the evidence for absolute benefit from screening of women younger than 50 years is weaker than

the evidence for older women, a mortality benefit for women aged 40-49 has still been shown in some clinical trials.

In the last two decades, ACR has independently reviewed the available evidence and recommended screening mammography for women who are 40 to 49 years old. The current update of the ACR guideline, revised in 1997, modified the screening interval from every 1 to 2 years to every year, stating that the recommendation "is justified by the more rapid growth of breast tumors among younger women." ACR concluded in their review that evidence from meta-analyses, using longer term follow-up, showed statistically significant mortality rate reductions of 18 to 29% for women 40 to 49 years old. In addition, they cite two randomized controlled trials demonstrating mortality rate reductions of 36% for women 45 to 49 years old at entry in Malmo, Sweden and 45% for women 39 to 49 years old at entry in Gothenburg, Sweden.

USPSTF's most recent (2002) recommendation concerning routine mammographic screening for women younger than age 50 is a change from its 1996 guideline, which found insufficient evidence to recommend for or against screening in this age group. The USPSTF has reviewed seven trials enrolling women aged 40-49, six of which were at least of "fair" quality. One of the trials was designed to specifically address benefits of screening in this age group and reported no reduction in breast cancer mortality with annual mammography and clinical breast examination. Of the remaining five trials, one reported significant mortality reductions, three non-significant mortality reductions, and one found no benefit. A meta-analysis pooling the results for women aged 40-49 in these six trials showed that the relative risk for breast cancer mortality was 0.85 (95% confidence interval 0.73-0.99) among screened women after 13 years of observation. These results are similar to prior meta-analyses based on older data. On average, the time until mortality benefits began to be observed was longer in women under 50 years than in older women. The analysis suggests that at least some of the mortality reduction was due to early detection of tumors before age 50.

CTFPHC's current (2001) recommendation for screening mammography in the 40 to 49 age group was modified from the 1999 version that recommended exclusion of women in this age group from screening mammography during the periodic health examination. The updated version neither recommends the inclusion of the maneuver in, or its exclusion from, the periodic health examination. This recommendation change is based on conflicting evidence regarding the benefits of screening women in this age group. They cite the Canadian National Breast Screening Study which did not show a reduction in mortality among women aged 40 to 49, and the two Swedish trials which showed a statistically significant benefit of screening mammography in subgroup analyses. CTFPHC stated that the most recent meta-analyses of 7 randomized controlled trials showed conflicting results. In one analysis, which included all 7 trials, a statistically significant relative risk reduction of 18% was shown, but a second analysis of only 2 trials found no effect.

RNZCGP also does not recommend routine screening for this age group because of the methodological problems in published studies. RNZCGP, however, does cite various meta-analyses showing mortality reductions ranging from 18-29% to 10% with screening mammography in women aged 40-49.

Although KPSC doesn't explicitly recommend routine screening for this age group, they recommend these women be informed of the benefits and harms of mammography and be "offered screening every one to two years." They cite a meta-analysis of 10 large, controlled trials that found a trend toward a 15% relative reduction in mortality risk in screened versus unscreened women aged 40-49.

Although SIGN includes a meta-analysis of the international screening mammography trials that showed statistically significant mortality reduction of 18 to 29% in the 40 to 49 age group, they do not make recommendations for routine screening in this age group. They, however, offer recommendations for annual mammography and clinical examination for women in the 40 to 50 age group who are at high risk of breast cancer.

Clinical Breast Examination (CBE)

The use of clinical breast examination (CBE) is another area in which the organizations disagreed. Much of the discord arises in whether CBE has any benefit when used alone. ACR recommends annual CBE, even though its benefit is not scientifically proven, because tumors can be found by this approach. SIGN recommends annual or more frequent CBE only in women at high risk for breast cancer. RNZCGP recommends that CBE be used in conjunction with mammography, since mammography is more sensitive than CBE alone in screening asymptomatic women, but the sensitivity of both combined is greater than either alone. RNZCGP also states that tumors detected by CBE tend to be larger than those detected by mammography, which has a bearing on mortality.

The additional effect of CBE on reducing breast cancer mortality beyond the benefit of mammography alone is therefore uncertain. USPSTF states that there is insufficient evidence to recommend for or against routine CBE alone to screen for breast cancer. They cite evidence that reductions in breast cancer mortality in studies using mammography alone are comparable to those using mammography plus CBE. No studies have been done comparing CBE alone to no screening. KPSC recommends CBE every 2-3 years beginning at age 20, although this guideline developer acknowledges there is no direct (but some indirect) evidence that CBE decreases breast cancer mortality.

Breast Self-examination (BSE)

There is general lack of agreement on the importance of breast self-examination (BSE) as a screening measure for breast cancer. Only two guidelines (ACR and SIGN) formally recommend BSE. SIGN acknowledges that there is no evidence to support BSE as a primary screening technique; however, because the majority of breast cancers are found by women themselves, SIGN believes that women should be encouraged to become familiar with the shape and feel of their breasts. ACR also believes it is prudent to recommend BSE, even though the benefit of BSE has not been scientifically proven. ACR's rationale is that small tumors are frequently found by either BSE or clinical breast examination. In contrast, CTFPHC maintains there is fair evidence of no benefit and good evidence of harm in teaching BSE to women aged 50 to 69 years and in women aged 40 to 49 years. CTFPHC was unable to make a recommendation for older women (•70 years) and younger women (<40 years) because of insufficient evidence. This current (2001)

statement was a modification of a previous (1999) recommendation that there was insufficient evidence to make a recommendation for or against teaching of BSE. In making this revision, CTFPHC specifically cites evidence from randomized controlled trials that showed an increase in the number of physician visits for evaluation of benign breast biopsies in women who were taught BSE. USPSTF concludes that there is insufficient evidence to recommend for or against teaching or performing BSE in any age group. USPSTF states that the accuracy of BSE is largely unknown, and that the available evidence shows a sensitivity of only 26-41% compared with clinical breast examination and mammography. KPSC and RNZCGP also do not recommend routine BSE because of a lack of evidence of clear benefit. Both groups, however, agree that women should be advised to report any breast changes that they detect themselves to their physicians. In addition, RNZCGP states that women should be advised to "regularly look and feel for breast changes rather than follow a systematic method of examination."

This Guideline Synthesis was prepared by ECRI on December 28, 1998. It was reviewed and verified by the guideline developers as of February 19, 1999. This Synthesis was modified by ECRI on April 12, 2001 to include guidelines from SIGN and CTFPHC. It was reviewed by these guideline developers as of May 24, 2001. This Synthesis was updated on September 19, 2001 to include a CTFPHC update. It was reviewed by CTFPHC as of October 8, 2001. This Synthesis was then updated on June 11, 2002 to incorporate new and updated KPSC, RNZCGP and USPSTF guidelines. Recommendations from ACPM, OMAR, and CTFPHC were also removed from this Synthesis following their withdrawal from the NGC Web site. This synthesis was updated again in 2002 to incorporate revised guidelines issued by USPSTF. In 2003, the 1997 ACS guideline was removed from this synthesis following the guideline's withdrawal from the NGC Web site.

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